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Delayed Termination Following Pacing Induced Shifts from Monomorphic to Polymorphic Ventricular Tachycardia: Implications for Antitachycardia Pacing

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Abstract— **Interactions between paced wavefronts and monomorphic ventricular tachycardia (VT) dictate antitachycardia pacing outcomes. Monomorphic VTs were initiated in isolated rabbit hearts (n = 6) that were endocardially cryoablated to limit viable tissue to the visible epicardium and the ablated apex served as an anatomic anchor. Preparations were optically mapped during single and dual site pacing at 50% to 90% of VT cycle length with 8 pulses per trial. Of these trials, responses to the 48 single site pulses and to the 172 dual site pulses that captured tissue were analyzed. Overall, we found most pulses reset the VT, and a small number of pulses that abruptly terminated the VT. Of particular interest, we found 12 pulses that shifted the anatomically anchored VT to functionally reentrant wavefronts, and thereby induced polymorphic VT. Delayed termination was observed following 6 of these instances, and the underlying non-sustained polymorphic VT's presented temporal characteristics similar to those presented by delayed termination after antitachycardia pacing in ICD patients.**

I. INTRODUCTION

Antitachycardia pacing (ATP) is an effective therapy for ventricular tachycardia (VT) that consists of a train of low energy pulses delivered through a right ventricular (RV) lead by an implantable cardioverter defibrillator (ICD) at a cycle length (CL) below that of the VT[1]. Conventional understanding of the mechanism by which ATP terminates monomorphic VT involves pacing during a cycle such that the orthodromic wavefront is blocked by the VT's refractory region, while the antidromic wavefront collides with the VT wavefront. Orthodromic wavefront block is often facilitated by earlier pulses in the ATP train that shift the VT's refractory region closer to the ICD pacing lead. When orthodromic wavefront block is achieved, the VT is extinguished if the antidromic wavefront either completely blocks the VT wavefront, or drives the combined antidromic-VT wavefront into inexcitable tissue. Such abrupt termination is attractive because it can increase the patients quality of life by preventing high energy shocks[1]. However, rate acceleration is still a concern. In addition, Sharma et al. recently documented an intermediate response, delayed termination, in which ATP shifted stable VTs to unstable VTs that extinguished after the pulse train [2]. The mechanism of delayed termination was not identified.

In the present report, we conducted optical mapping experiments with rabbit hearts in which viable tissue was restricted, primarily, to the visible epicardium, but was still of sufficient area to enable complex interactions between paced wavefronts and the VT's wavefront or refractory region. With this protocol we identified pulses that shifted anatomically anchored monomorphic VT to polymorphic VT by creating intersections of depolarizing tissue and repolarizing tissue, which do not exist during normal conduction or anatomically anchored VT. Such intersections of depolarizing and repolarizing tissue are a hallmark of functional reentry, and the mechanism by which such intersections were induced in this preparation is consistent with the theory of spiral wave generation as described by Arthur Winfree[3]. Many of these instances of polymorphic VT were non-sustained, and possessed temporal characteristics similar to those documented by Sharma et al.

II. METHODS

A. Isolated Rabbit Heart Preparation

Six New Zealand white rabbits (2.8 to 3.6 kg) were anesthetized with ketamine (44 mg/kg) and xylazine (10 mg/kg), then euthanized with nembutol (150 mg). The hearts were quickly excised. The aorta was cannulated for retrograde perfusion with Tyrode solution (38° to 39°C) equilibrated with 95% O_2 and 5% CO_2. The composition of Tyrode solution was (in mmol/L) NaCl 121.32, glucose 21.98, $MgCl_2$ 0.98, KCl 4.40, taurine 19.98, creatine 4.99, $C_3H_3O_3Na$ 5.00, NaH_2PO_4 1.01, $CaCl_2$ 1.08, and $NaHCO_3$ 28.57. A thin wall of ventricular epicardium was created by immersing the heart in a 37°C bath of Tyrode solution, and inserting a liquid nitrogen filled cryoprobe through an incision in the left atrium and into the left ventricle for 225 s. The probe was then inserted through an incision in the right atrium into the right ventricle for 45 s. The atria, ventricular endocardium, ventricular midwall, ventricular septum, and apical epicardium were affected by the cryoprocedure. Fig. 1A shows the triphenyl tetrazolium chloride (TTC, 42mmol/L) stained heart from one experiment. TTC stains viable tissue red, leaves ablated tissue brown, and the cross sectional image reveals that cryoablation limited viable tissue to the epicardium[4]. The solid arrows mark the border between

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viable and ablated tissue near the ventricle base, and the open arrows mark that border near the apex.

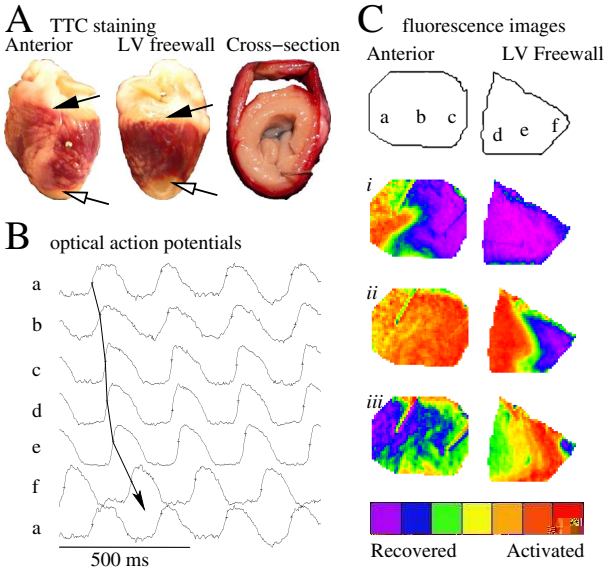

Fig. 1. (A) TTC stained preparation from anterior, LV free wall, and cross-sectional views. (B) Optical action potentials during monomorphic VT prior to pacing in the preparation shown in (A). (C) Preparation schematic and fluorescence images during the cycle highlighted in (B). Frames *i-iii* were acquired at the maximal upstroke times at sites b, e and f, as marked in the schematic, respectively.

B. VT Induction

Following cryoablation, the heart was suspended in a constant flow (50 ml/min) Langendorff perfusion system for optical mapping. Diacetyl monoxime (DAM, 20 mmol/L) was added to the perfusate to eliminate contraction artifacts during mapping. Hearts were stained with voltage sensitive dye (di-4-ANEPPS, 10 μmol/L). Two digital charge coupled device cameras (MiCAM 01 ICX-082, Brainvision Inc., Japan) recorded fluorescence at 96 $\times$ 64 pixels (500 frames/second) simultaneously from the anterior face of the ventricles and the LV free wall. VT was established by burst pacing through either the LV or RV epicardial electrode, and monitored for stability via coil electrodes placed in each ventricular cavity. Stable monomorphic VT was always anchored to the apical infarct, and traversed the epicardium such that the pacing electrodes were within the circuit. Fig. 1B shows optical action potentials from six sites (a-f) recorded for 1 second during stable (CL = 251$\pm$7 ms) monomorphic VT in one experiment. The sites were selected to form a ring around the visible epicardium, and the arrow illustrates the activation sequence through one cycle. Fig. 1C shows fluorescence images from anterior and LV free wall views during the cycle highlighted by the arrow in Fig. 1B. The top frame is a schematic showing the locations of recording sites. In subsequent frames, fluorescence is encoded on a red-yellow-blue color scale, with red indicating activated tissue, and blue indicating recovered tissue. These frames show wavefront travel around the ventricles at times corresponding to maximum optical action potential upstrokes at site b (frame *i*), site e (frame *ii*), and site f (frame *iii*). VT CLs across all preparations ranged from 234$\pm$34 ms to 470$\pm$67 ms. All monomorphic VTs were highly stable.

C. Pacing

We used a train of 8 pulses (10 mA strength and 5 ms duration) applied through the RV lead (single site) or both the RV and LV leads (dual site) for each trial. We adjusted the coupling interval from 50% to 90% of VT CL in 10% increments in different trials. When pacing failed to capture, or simply reset the VT, we allowed 1 min for the VT to stabilize before initiating a new trial. If pacing terminated the VT, monomorphic VT was re-established by burst pacing, and allowed to stabilize before a new trial.

III. Results

A. Polymorphic VT induction

We identified 12 pulses that caused a transition from an anatomically anchored VT to a VT with a functional center. This transition resulted during trials in which the region where the antidromic wavefront initially collided with the VT wavefront recovered excitability before the combined antidromic-VT wavefront was extinguished on the inexcitable boundaries. The newly recovered region then served as a path for a functionally reentrant wavefront during the initiating cycle of polymorphic VT. Polymorphic VT induction was observed with 10% (5 of 48) and with 4% (7 of 172) of pulses that captured tissue during single and dual site pacing, respectively. Partial capture accounted for 6 of the 7 pulses during dual site pacing, such that 11 of these 12 trials captured at only one site. A single wavefront traveled around the line of block following 8 of these pulses.

Fig. 2A shows fluorescence images from a trial in which single site pacing at 70% of VT CL established this response. Frames are shown at 40 ms intervals following pulse 4, with frame *i* acquired 30 ms following pulse delivery. Only images from the anterior view are shown because the LV free wall acted as a bystander during this trial. Frame *i* shows that the pulse captured tissue around the pace site (white circle) as the VT (grey arrow) approached from the RV free wall. The paced antidromic wavefront (black arrow) collided with the VT wavefront in the region of frame *ii* marked with a white dashed line, but did not achieve complete antidromic block. In addition, the paced orthodromic wavefront was blocked on the VTs refractory region, as evidenced by the lack of expansion from the pace site, and the portion of the orthodromic wavefront block that is highlighted by the dashed black line served as a functional center for the merged antidromic-VT wavefront, as shown in frames *iii* and *iv*. Frame *iv* also shows that the region of initial collision of the antidromic and VT wavefronts had recovered excitability and would subsequently serve as the path for the functionally reentrant wavefront. Although subsequent pulses 5 and 8 captured tissue, the established wavefronts were unable to penetrate the functional center (not shown).

The other 4 of 12 trials established figure-of-eight reentry when wavefronts pivoted around the line of conduction

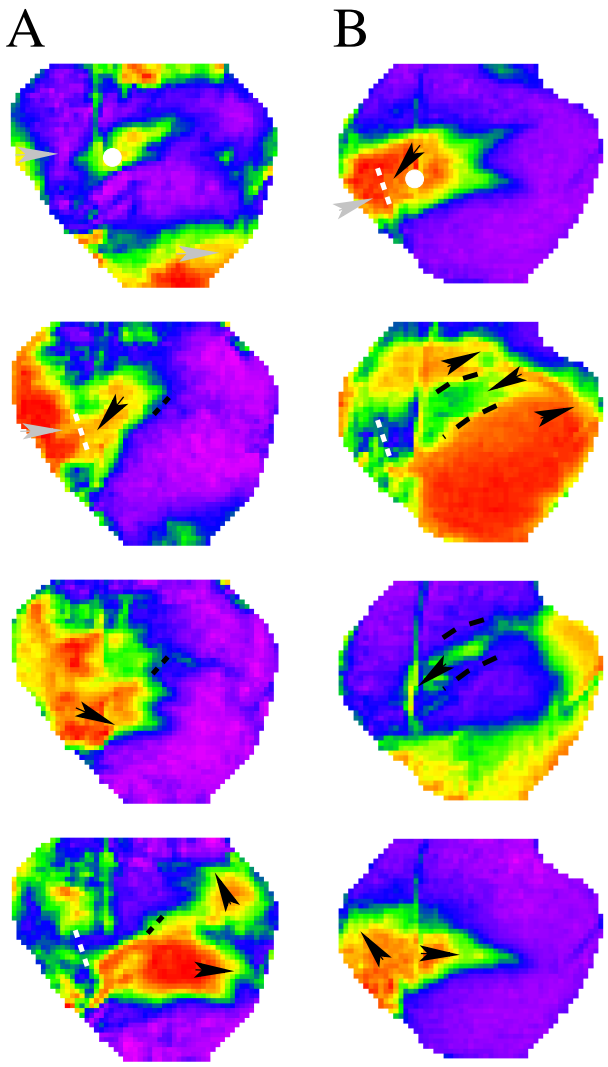

Fig. 2. Initiation of polymorphic VT. Grey arrows show the direction of the VT wavefront, and black arrows show the direction of paced wavefronts. White dashed lines represent regions where the VT wavefront collided with the antidromic wavefront. Black dashed lines represent the paths of functional center of the wavefront for the first cycle of functional reentry. (A) Induction of polymorphic VT that consisted of a single reentrant circuit during single site pacing at 70% of the VT CL. Frames are at 40 ms intervals. (B) Induction of polymorphic VT that consisted of a figure-of-eight reentrant circuit during single site pacing at 50% of the VT CL. Frames are at 80 ms intervals.

block in both the apical and basal regions. Fig. 2B shows fluorescence images from a trial in which single site ATP at 50% VT CL induced this response. Again the LV free wall is not shown because it acted only as a bystander in this trial. Frame *i* was acquired 82 ms after pulse 7 was delivered, and the white dashed line marks the region where the VT wavefront (grey arrow) collided with the paced antidromic wavefront (black arrow). The refractory tissue behind the VT wavefront prevented orthodromic wavefront expansion, but did recover excitability in time to permit the merged antidromic-VT wavefront to expand in this tissue region. Subsequent frames are shown at 80 ms intervals. Frame *ii* shows that the merged antidromic-VT wavefront expanded in the orthodromic direction, but did not penetrate the region of tissue marked with the dashed black lines. This frame also shows that the region where the antidromic wavefront originally collided with the VT wavefront had recovered excitability and enabled the figure-of-eight reentrant wavefronts to complete their first cycle, as shown in frames *iii* and *iv*, with the tissue between the black lines serving as the central common pathway.

B. Temporal characteristics of delayed termination

Following the 12 pulses that induced the transition from monomorphic VT to polymorphic VT, we observed a return to monomorphic VT in 2 trials, sustained polymorphic VT that we terminated with shocks in 4 trials, and nonsustained polymorphic VT that eliminated all electrical activity in 6 trials. These outcomes did not depend on the number of functional circuits. Optical action potentials from sites that formed a ring around the tissue at medial height in the preparation were used to determine temporal characteristics of VTs. Fig. 3 shows 4 such sites from one of the trials with non-sustained polymorphic VT. Fig. 3A shows optical action potentials during pacing (labeled 1-8), and afterward. Measured CLs are marked in the post-pacing interval in Fig. delayedtermB. During pacing, CLs measured $256+/-10$ ms, but following pacing they measured $250+/-60$ ms. Defined by Sharma et al. as the increase in standard deviation of mean CL, VT variability was therefore (60/10) = 600%, for an increase of 500% in this example. Over all 6 trials with non-sustained polymorphic VT, the number of cycles measured $4.2+/-3.5$, and the mean CL variability increased by 146%. These results are strikingly similar to Sharma et al.'s findings of 5.4 ± 3.1 VT cycles after ATP with a 150% increase in CL variability that preceded delayed termination.

IV. Discussion

We undertook the present study to assess interactions between paced wavefronts and monomorphic VT to improve understanding of antitachycardia pacing. ICDs are increasingly used to treat fast VT, as well as slow, hemodynamically tolerated VTs, and improved understanding could lead to further improvement of arrhythmia management through improved pacing algorithms or optimal use of an LV lead. One important step is identifying the conditions under which ICDs accelerate rather than terminate arrhythmias. We demonstrated that, in tissue, pacing can shift the VT off its anatomic anchor when the antidromic wavefront fails to drive the VT wavefront into inexcitable tissue. Though such a shift has long been assumed to underlie ATP induced rate acceleration, confirmation is not currently possible in clinical studies because ICDs provide electrical recordings that are restricted to the lead sites, and do not provide information about the repolarization period. We are the first to clearly demonstrate this mechanism during pulse trains in epicardial tissue with an optical mapping technique that illustrates tissue depolarization as well as repolarization with high spatial and temporal resolution. Perhaps most important, though, are the similarities between the temporal characteristics of

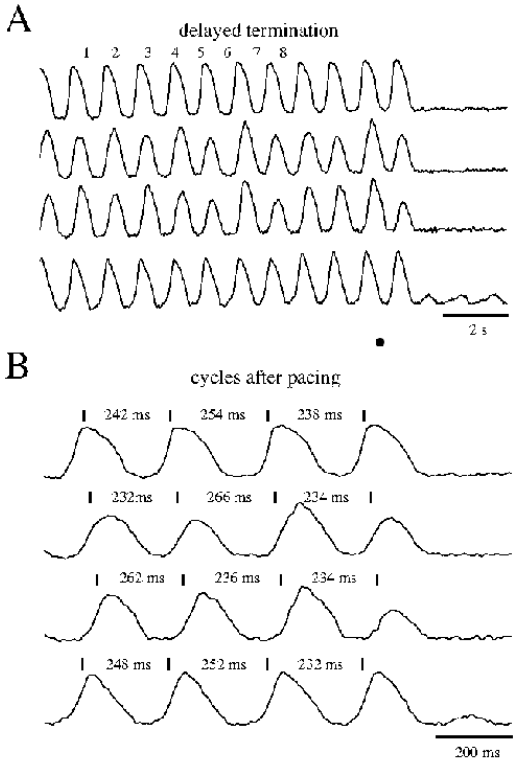

Fig. 3. (A) Optical action potentials from one episode of delayed termination. (B) Waveforms from (A) detailing the 3 cycles following ATP. The CLs of each interval are marked.

delayed termination in this preparation, and those recorded in coronary artery disease patients [2]. In that report, the authors hypothesized that delayed termination could result from a transition from a path around an anatomic anchor to multiple pathways available in the three-dimensional medium of the heart. Although our preparation was limited in the transmural dimension, our results support this hypothesis.

REFERENCES

[1] M. Wathen, P. DeGroot, M. Sweeney, A. Stark, M. Otterness, W. A. R. Canby, K. Khalighi, C. Machado, D. Rubenstein, and K. Volosin, "Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter defibrillators," *Circulation*, vol. 110, no. 17, pp. 2591 – 2596, 2004.

[2] V. Sharma, P. DeGroot, and M. Wathen, "Incidence and characteristics of type-2 breaks in response to antitachycardia pacing therapy in implantable cardioverter defibrillator patients," *J Cardiovasc Electrophysiol*, vol. 14, no. 11, pp. 1156–1162, Nov. 2003.

[3] A. Winfree, *When time breaks down*. Princeton, NJ: Princeton university press, 1987.

[4] M. Schalij, W. Lammers, P. Rensma, and M. Allessie, "Anisotropic conduction and reentry in perfused epicardium of rabbit left ventricle," *Am J Physiol*, vol. 263, no. 5 Pt 2, pp. H1466– H1478, Nov 1992.